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Letter to the Editor

Efficacy and safety of isoniazid preventive therapy in light of increasing multi-drug resistance in tuberculosis

Tuberculosis (TB) has emerged as a major warning to global public health as 33% of the world population is considered to be infected with *Mycobacterium tuberculosis* (MTB). Further, multi-drug-resistant strains of MTB in association with human immunodeficiency virus (HIV) have further created a worrying aspect to the TB problem. The current epidemics of extensively drug-resistant TB have also been an increasing threat in some regions around the world [1]. Most drug-resistant clinical strains of MTB, are resistant to isoniazid (INH), one of the most effective anti-TB drugs used for TB treatment [2]. Since existing TB control methods seem inadequate to prevent the rise in TB incidence among HIV-infected persons, the World Health Organization recommends INH preventive therapy (IPT) for HIV-infected persons as part of the core services [3].

Although two recent meta-analyses have shown that there was more than a 60% reduction in TB in HIV-infected adults after IPT [4], another meta-analysis study also reported that INH prophylactic therapy was not so much effective among young children and that there was little evidence of a mortality benefit in children of any age [5]. After conducting a systematic review on IPT and risk for resistant TB, Balcells et al. [6] suggested that IPT therapy would decrease the number of reactivated TB cases attributable to INH-susceptible strains but would have a lesser effect on resistant strains, which would increase the proportion of resistant strains among subsequent cases of active TB. Further, they suggested that the presence of active TB should be excluded before IPT, and continued surveillance for INH resistance is essential [6]. INH is reported to generate a variety of highly reactive compounds, such as reactive oxygen species like superoxide, peroxide and hydroxyl radical, nitric oxide, reactive organic species like isonicotinicacyl radical or anion, and certain electrophilic species, which then attack multiple targets in MTB. INH is a prodrug and requires activation before it becomes therapeutically effective. This process is carried out by the catalase-peroxidase activity of the *katG* gene product, and mutations in the *katG* gene contribute to resistance to INH [7]. Bioinformatics studies in our laboratory showed that a mutation in *katG* (S315T/S315N) prevents free radical formation, thus the development of resistance to the drug [8] and mutation in N-acetyltranserase enzyme which has an important role in acetylating and detoxifying INH, increases the stability and catalytic ability of the mutant enzyme, thus making the drug ineffective (unpublished data). As per the TB drug resistance mutation database, 22 genes/proteins of MTB were reported to associate with INH resistance [9]. Out of 22 genes/proteins, 11 genes were reported to be induced by INH [10]. The detailed mechanism of resistance and induction in a number of proteins is yet to be thoroughly understood. Thus, there is a need to understand the role of INH inside the host as well as in MTB in order for the drug to be used widely in preventive therapy of TB, for the fear that one day it may not become effective in TB therapy.

INH is not a safe drug and is not without toxicity and side effects. Adverse effects of INH have been reported by different researchers based on their clinical studies. INH, alone or in combination with other anti-TB drugs, mostly associated with toxicity [11]. Acute poisoning leads to lactic acidosis and renal failure [12], development of agranulocytosis [13], INH-induced tenosynovitis [14], INH-induced liver injury [15,16], and fatal INH-induced acute liver failure [17] are a few of the toxic consequences of INH. Furthermore, INH and/or its metabolites (e.g., hydrazine) may be associated with causing mitochondrial injury that may lead to oxidant stress in mitochondria and destruction of energy homeostasis [15]. Cataño and Morales [18] studied the follow-up results of INH chemoprophylaxis during biological therapy in Colombia and observed that 3.2% of patients developed active TB, and 17.2% of patients developed intolerance or toxicity related to INH. Based on their observation they suggested that chemoprophylaxis with INH seems to be effective and safe for the prevention of most TB reactivation in individuals with latent TB infection, but toxicity must be monitored during follow-up [18]. However, concerns have been raised about the wide use of INH due to its toxicity, predominantly hepatotoxicity, as biochemical monitoring is not routinely carried out during INH therapy [17].

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Although IPT is increasingly recommended for preventing TB in healthy children and treating latent TB infection in HIV patients, concerns about the risk for development of INH-resistant TB with extensive use of INH should be considered before its widespread use in HIV infection, latent infection, and in particular in children.

Conflicts of interest

All authors have no conflicts of interest to declare.

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Lingaraja Jena
Bhaskar C. Harinath*
Bioinformatics Centre, JBTDRC, MGIMS, Sevagram, Maharashtra, India
* Corresponding author at: JB Tropical Disease Research Centre, Mahatma Gandhi Institute of Medical Sciences, Sevagram 442 102 (Wardha), Maharashtra, India.
E-mail addresses: bc_harinath@yahoo.com, info@jbtdrc.org (B.C. Harinath)

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